Urologia Internationalis

Urol Int 1999;63:87–91

Review

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Brachytherapy for Prostate Cancer

Introduction

During the last decade, prostate cancer has become the most common malignancy in men in the United States, and in Germany it is already the second most common malignant tumour diagnosed in men. This absolute and relative increase in the incidence of prostate cancer in the developed industrialized nations is due to several factors. First, a still rising life expectancy and an already high prevalence of latent prostate cancer in the elderly population lead to a growing population of relatively healthy septuagenarians and even octogenarians who live long enough to experience prostate cancer.

Secondly, the diagnosis of prostate cancer has been greatly improved by the usage of prostate-specific antigen (PSA) and ultrasound-guided prostate biopsies. The widespread use of these two tools in addition to the traditional doctor's palpating finger has brought an absolute increase in the incidence of prostate cancer in many countries where medical services are easily available. PSA and prostate biopsies have also led to a diagnostic shift towards the earlier diagnosis of more organ-confined stages in younger patients.

It is clear that organ-confined tumours in relatively young patients in their sixties or even fifties should be aggressively treated. Due to the advances which radical surgery has made, radical prostatectomy is today the first-line treatment option for most patients in this age group. However, the older age group will not necessarily be candidates for radical prostatectomy. Radiotherapy as an alternative to radical surgery has always been advocated as a less invasive, more easily tolerated treatment for prostate cancer. However, percutaneous external beam radiotherapy (EBRT) has by necessity side effects and complications arising from radiation to the organs and tissues surrounding the prostate which can be bothersome.

For this reason the concept of trying to focus radiation on the prostate as much as possible in order to reduce the radiation dose delivered to the bladder, the urethra and the rectum has long been a major concern for radiotherapists. Three-dimensional conformal planning and oscillating radiation fields have been improvements in EBRT which address just this issue.

Brachytherapy

Another way to achieve maximum radiation focussing on the prostate is interstitial radiotherapy (brachytherapy). With brachytherapy, radioactive particles (seeds) are brought into the target organ or tissue thus bringing the radiation source directly into the tissue. Implantation can be temporary or permanent, and organs which lie relatively superficial to the body surface are amenable to interstitial radiotherapy (uterine cervix, breast, head and neck tumours). The use of brachytherapy dates back to the beginning of this century when soon after the discovery of radioactivity, radioactive materials and their potential uses were introduced into clinical medicine.

Thus, brachytherapy as a treatment for prostate cancer began in 1911 when Pasteau described the implantation of radium isotopes using a transurethral catheter. In 1922, Denning published the results of 100 patients with prostate cancer treated by this method. However, results were not satisfactory, and this treatment modality was not developed further at the time.

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0042–1138/99/0632–0087$17.50

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Brachytherapy for prostate cancer was rediscovered in the 1950s when gold isotopes became readily available [1]. The implantation technique before the era of ultrasonography remained a problem, and in the 1970s the open surgical implantation of ^{125}I seeds using the retropubic access was used by Hilaris et al. [2]. However, transurethral seed dislocation and lack of control of seed positioning remained problematic issues with this method and the rate of tumour control with 'hot' and 'cold' spots in the prostate was disappointing [3, 4]. Long-term follow-up of patients treated by this method showed disappointing 10-year survival rates [5] and revealed that the only significant prognostic factor which could be identified was the absence or presence of lymph node metastases at the time of treatment. The therapeutic benefit of this technique was therefore disnounced by Whitmore and co-workers [6] in 1982.

Today we experience another renaissance of brachytherapy for prostate cancer. There are several reasons for this. First, with the epidemiological shift in the age structure of our populations and the increased incidence of prostate cancer brought about by advances in clinical urology, we are today faced with a larger than ever number of prostate cancer patients who need and want treatment. However, a significant proportion of these are not good candidates for surgery and also, an increasing number of patients opt for minimally invasive treatment. Secondly, the radioactive seeds which are today commercially available have better radiation characteristics in terms of radiation dose and half-lives. Thirdly, modern imaging techniques allow precise pretreatment dosimetry, better seed positioning and posttreatment dosimetry evaluation. All this was not possible before the use of high-quality transrectal ultrasound and computerized tomography. With these new possibilities several problems encountered with the method in the past, such as 'stranded seeds' [4], can be expected to have been solved and modern brachytherapy for prostate cancer may well have to offer advantages to patients and urologists.

Technique of Prostate Brachytherapy

Modern brachytherapy depends on the use of transrectal ultrasonography, computerized dosimetry planning systems and application devices (templates) which can be fixed in a stable position relative to the perineum.

Two principally different approaches to brachytherapy of the prostate are possible: permanent seed implantation using isotopes with low energy and short half-lives (^{125}I,^{198}Au, ^{103}Pd) [7] or the temporary afterloading technique (^{192}Ir) whereby radioactive sources placed on needles are brought into the prostate for a short period and removed thereafter. The afterloading technique is usually applied in combination with EBRT and requires the technical installations of great sophistication and costs needed for intraoperative radiotherapy application.

Permanent seed implantation is technically much easier to implement and perform and therefore receives most interest at present. Holm [8] described a technique of transrectal ultrasound-guided perineal implantation of ^{125}I seeds in 1983. This technique has become the standard approach although several modifications and refinements have been described by several other groups [9–11].

^{103}Pd has become commercially available as an implantable isotope seed since 1988 and since that time has been used for prostate brachytherapy by several North American radiotherapy centres [12]. ^{103}Pd has a mean half-life of 17 days with a mean energy of 21 keV, corresponding to an initial radiation dose of 20–30 cGy. In comparison, ^{125}I has a half-life of 60 days, a mean energy of 28 keV and an initial dose rate of 5–10 cGy. The advantage of ^{103}Pd is therefore that it can deliver a higher energy dose per volume with a shorter half-life.

The technique of permanent seed implantation into the prostate depends on three main elements: conformal dosimetric planning based on high-quality imaging using CAT scanning or transrectal ultrasound, real-time image-controlled anatomical seed implantation based on transrectal ultrasound or fluoroscopy and posttreatment dosimetric control of seed positioning again using CAT scans. There are only minor variations between the techniques used by different institutions.

The exact pretreatment planning requires the computerized anatomical measurement of the volumes of the prostate, the urethra and the rectum in order to determine the correct target radiation doses. These lie around 140–160 Gy for monobrachytherapy with ^{125}I and around 115–120 Gy with ^{103}Pd [13]. If brachytherapy is used in conjunction with EBRT, much lower doses are required. The perineal templates used for needle positioning limit the distance between the needles to a minimum of 0.5 cm. Usually a minimum of 1 cm is observed.

There is no agreement between different institutions about the distribution of the total radiation dose within the prostate. Some prefer a homogeneous dose distribution with only 10–15% of the total dose applied to the periphery of the prostate thus minimizing the radiation dose which is delivered to the rectum and the urethra [14, 15]. Others prefer to apply 70% of the total dose to the prosta-

tic periphery where most carcinomas arise, taking into account that more radiation dose will be delivered to the rectum [11, 16].

One problem of this mode of brachytherapy is that the actually administered radiation dose is still variable despite the use of real-time imaging and dosimetry. With a target dose of 140–160 Gy, posttreatment dosimetry evaluation can show variations from 30 to 260 Gy [17]. This will have obvious implications for the therapeutic efficacy as does the problem of stranded seeds encountered with this technique. Possibly the new three-dimensional imaging techniques that now become available can improve these problems [18].

The procedure does require some form of anesthesia and can be done under general or spinal anesthesia. While some urologists advocate an outpatient application of brachytherapy, generally most of the elderly patients for whom this technique is designed [19] require a hospital stay of 2–3 days [19]. For the procedure the patient is placed in a lithotomy position and a transurethral catheter should be inserted in patients with a large gland.

Posttreatment dosimetry is essential in assessing the quality of seed implantation. CAT scanning is used to visually identify the implanted seeds, and isodose curves are calculated for each CT image. Problems due to postoperative oedema especially near the prostatic apex and due to image artefacts caused by the metallic seeds can arise, and may partially explain the great variation that can occur between target dosimetry and posttreatment dosimetry [17]. Posttreatment dosimetry also allows for secondary brachytherapy application in case of underdosage or large 'cold spots'.

The side effects and complications caused by brachytherapy for prostate cancer are usually minimal or moderate [14, 20–22]. Urethral symptoms of dysuria are the rule rather than an exception but are mostly mild and disappear within weeks or months [22]. Acute urinary retention does occur in patients with pretreatment obstructive symptoms and large glands due to oedema of the prostate in 8–15%. Symptoms of proctitis occur in 1–9%, more frequently (up to 12%) with longer follow-up, and will be more common when the prostatic periphery is preferentially loaded. Incontinence following brachytherapy is uncommon and is seen usually only in patients that have undergone transurethral resection before or after brachytherapy. Erectile dysfunction after brachytherapy is reported in 6–28% [13, 22–24] and usually increasing with time. As with other forms of treatment for prostate disorders, posttreatment erectile function is related to the patient's age and general health [25]. Severe complications are rare but some, such as urethrorectal fistula formation [22], have been reported.

However, the evaluation of brachytherapy as a treatment modality for prostate cancer will foremost depend on its curative efficacy. The slow rate of proliferation and the long natural disease course of 10–15 years make the assessment of any treatment for prostate cancer difficult. Useful end-points of follow-up studies must not only be overall survival but also progression-free survival and biochemical evidence of progression-free survival. As with EBRT, evidence of residual disease can be assessed by posttreatment biopsies although the interpretation of findings and their relevance can be difficult.

In short-term studies, posttreatment PSA assessment has revealed progression-free survival for ^{103}Pd and ^{125}I brachytherapy of 86, 88 and 76% [20, 21, 26]. However, the definitions used for biochemical progression-free survival are not uniform and thus difficult to compare: PSA <1 ng/ml after 4 years [20], PSA <4 ng/ml after 3 years [21], and PSA without rise after reaching a nadir after 2 years [26]. Clearly, these figures are difficult to interpret and will depend on pretreatment PSA as well. Furthermore, the follow-up periods are as yet far too short to assess long-term efficacy adequately.

As with EBRT, brachytherapy as a treatment modality suffers from the drawback that in contrast to radical prostatectomy, PSA-related definition of cure is uncertain. Furthermore, PSA-persistence and even PSA progression do not necessarily mean persistence or progression of the prostate cancer. However, for all raidotherapeutic treatment modalities, a low PSA nadir (<0.2 ng/ml) is desirable and of prognostic significance [27].

Post-treatment biopsies of the prostate after brachytherapy are not reliable in assessing curative efficacy. They should not be done before at least 18 to 24 months after brachytherapy have elapsed because due to the radiation effect on the mitotic phase of carcinoma cells, the induced cell death will be prolonged. Furthermore, post-radiation biopsies of the prostate are difficult to interpret and errors can occur. For this reason an 'intermediary' category with the need for later re-biopsies is now acknowledged when assessing post-treatment biopsies for residual cancer after brachytherapy [13, 28]. A further caution must be added in that according to Whitmore a negative biopsy simply signifies the absence of proof of persistence, not necessarily cure [29]. The possibility of radiation resistance of undifferentiated or anaplastic prostate cancer cells may be a factor contributing to the heterogeneity of results reported for brachytherapy [30].

There are still very few data from long-term follow-up on the curative efficacy of modern brachytherapy for prostate cancer. Several groups report favourable outcome data and claim a PSA relapse-free survival similar to that achieved by radical surgery in similar patients [31–33]. Ragde et al. [34] reported a PSA-progression-free survival of 79% after seven years for patients with organ-confined (T1/T2) prostate cancer. Polascik et al. [35] contrast this finding with a matched pair analysis showing a much higher PSA relapse-free survival rate after seven years following radical prostatectomy. In other studies the relative risk of a PSA progression after brachytherapy was also found to be higher in comparison to radical prostatectomy [36].

The assessment of brachytherapy in its ability to cure prostate cancer in comparison to other treatment modalities is at present not possible. Only long-term follow-up studies of at least 10 years' duration will be able to answer some of the questions. Survival and progression-free survival data with a median follow-up of 18–37 months which are available at present are not adequate information on which definitive assessment should be based [12, 13].

In summary, although brachytherapy for prostate cancer is nothing new, modern brachytherapy with high-quality imaging and dosimetry offers new dimensions and thus a treatment modality for prostate cancer that potentially will achieve great importance in the treatment of elderly patients with organ-confined or even locally advanced tumours. However, at present we cannot with safety make statements about the curative efficacy of brachytherapy for prostate cancer.

The low rate of complications and the ease of its applicability have led some centres to a great enthusiasm about brachytherapy. Patients are often easily impressed with simple procedures of low invasiveness. However, as urologists we must be aware that at present data show a better therapeutic efficacy for radical prostatectomy. Thus, so far there is no proof that brachytherapy is as effective in curing prostate cancer as radical prostatectomy is. Until this proof is obtained, it should not be assumed to be the case. Overemphasizing the benefits of short hospital stay and low rate of complications can mislead both patients and doctors since a low rate of complications reported may not necessarily be reproducible elsewhere where this procedure is less frequently performed. Until more is known from controlled studies about the long-term efficacy and complications of brachytherapy for prostate cancer, caution is advisable.

References

1 Flocks RH, Kerr HD, Elkins HB: Treatment of carcinoma of the prostate by interstitial radioactive gold. J Urol 1952;68:510.
2 Hilaris RS, Whitmore WF, Batatata MA, Grabstald H: Radiation therapy and pelvic node dissection in the management of cancer of the prostate; in Hilaris RS (ed): Handbook of Interstitial Brachytherapy, Boston, Acton, 1975, p 219.
3 Sogani PC, DeCrosse JJ, Montie J: Carcinoma of the prostate. Treatment with pelvic lymphadenectomy and iodine-125 implants. Clin Bull 1979;9:24.
4 Sommerkamp H, Rupprecht M, Wannenmacher M: Seed loss in interstitial radiotherapy of prostatic carcinoma with I-125. Int J Radiat Oncol Biol Phys 1988; 14:389–392.
5 Fuks A, Leibel AA, Wallner KE, et al: The effect of local control on metastatic dissemination in carcinoma of the prostate: Long-term results in patients treated with 125-iodine implantation. Int J Radiat Oncol Biol Phys 1991;21:537–547.
6 Grossman HB, Batata M, Hilaris B, Whitmore WF: 125-Iodine implantation for carcinoma of the prostate: Further follow-up of first 100 cases. Urology 1982;20: 591–598.
7 Butler EB, Scardino PT, Teh BS, Uhl BM, Guerriero WG, et al: The Baylor College of Medicine experience with gold seed implantation. Semin Surg Oncol 1997; 13:406–418.
8 Holm HH: Transperineal iodine-125 seed implantation in prostate cancer guided by transrectal ultrasonography. J Urol 1983;130:283.
9 Ragde H, Blasko JC, Schumacher D: Use of transrectal ultrasound in transperineal iodine-125 seeding for prostate cancer: Methodology. J Endourol 1989;3:209.
10 Kaye KW, Olson DJ, Lightner DJ: Improved technique for prostate seed implantation: Combined ultrasound and fluoroscopic guidance. J Endourol 1992;6:61.
11 Stock RG, Stone NN, Wesson MF: A modified technique allowing interactive ultrasound-guided three-dimensional transperineal prostate implantation. Int J Radiat Oncol Biol Phys 1995;32:219.
12 Brosman SA, Tokita K: Transrectal ultrasound-guided interstitial radiation therapy for localized prostate cancer. Urology 1991;38:372–376.
13 Blasko JC, Ragde H, Luse RW, Sylvester JE, Cavangh W, Grimm PD: Should brachytherapy be considered a therapeutic option in localized prostate cancer? Urol Clin North Am 1996; 23:633–650.
14 Kaye KW, Olson DJ, Payne JT: Detailed preliminary analysis of 125-iodine implantation for localized prostate cancer using percutaneous approach. J Urol 1995;153:1020.
15 Grimm PD, Blasko JC, Ragde H: Ultrasound-guided transperineal implantation of iodine-125 and palladium-103 for the treatment of early-stage prostate cancer: Technical concepts in planning, operative technique and evaluation. Atlas Urol Clin North Am 1994; 2:113.
16 Wallner K, Chiu-Tsao S, Roy J: An improved method for computerized tomography-planning transperineal 125-iodine prostate implants. J Urol 1991;146:90.
17 Stock RG, Stone NN; Tabert A, Ianuzzi C, DeWyngaert JK: A dose-response study for I-125 prostate implants. Int J Radiat Oncol Biol Phys 1998; 41:101–108.
18 Koutrouvelis PG: Three-dimensional stereotactic posterior ischiorectal space computerized tomography guided brachytherapy of prostate cancer: A preliminary report. J Urol 1998;159:142–145.
19 Cash JC, Dattoli M: Management of patients receiving transperineal palladium-103 prostate implants. Oncol Nurs Forum 1997;24:1361–1367.

20 Stock RG, Stone NN, DeWyngaert JK: PSA findings and biopsy results following interactive ultrasound-guided transperineal brachytherapy for early-stage prostate cancer. Proc 78th Annual Meeting of the American Radium Society, Paris, 1995.
21 Blasko JC, Ragde H, Grimm PD: Transperineal ultrasound-guided palladium-103 brachytherapy for prostate carcinoma (abstract). J Urol 1995;153:385.
22 Al-Booz H, Ash D, Bottomley DM, Carey BM: Short-term morbidity and acceptability of 125-iodine implantation for localized carcinoma of the prostate. Br J Urol 1999;83:53–56.
23 Benoit RM, Cohen JK, Miller RJ, Naslung MJ: Complications and adjuvant treatment after prostate brachytherapy. J Urol 1998;159 (suppl):63, abstr 235.
24 Scherr D, Bosworth J, Potters L, Waldbaum R, Steckel J: Complications of brachytherapy in 692 men treated for localized prostate cancer. J Urol 1998;159(suppl):65, abstr 243.
25 Flanders S, Henning JM, Lubeck DP, Pasta DJ, Stoddard ML, Litwin MS: A multivariate analysis of sexual function and bother in men treated with prostatectomy or irradiation for early stage prostate cancer: Quality of life results from the CAPSURE database. J Urol 1998;159(suppl): 219, abstr 847.
26 Grado GL, Larson TR, Collins JM: Fluoroscopic and ultrasound-guided prostate implant: Technique and experience at Mayo Clinic Scottsdale (abstract). Proc 18th Annual Meeting of the American Brachytherapy Society, Scottsdale, Ariz., 1995.
27 Critz FA, Levinson AK, Williams WH, Holladay DA, Holladay CT, Griffin VD: The PSA nadir goal for radiotherapy of prostate cancer is smaller than or equal to 0.2 ng/ml. J Urol 1998;159(suppl):219, abstr 844.
28 Prestidge BR, Hoak DC, Grimm PD, Ragda H, Cavangh W, Blasko JC: Posttreatment biopsy results following interstitial radiotherapy in early-stage prostate cancer. Int J Radiat Oncol Biol Phys 1997;37: 31–39.
29 Grossman H: Summary of 125-iodine implantation for carcinoma of the prostate: Further follow-up of first 100 cases. Semin Urol Oncol 1997;15:111–114.
30 Fuks A, et al: The effect of local control on metastatic dissenmination in carcinoma of the prostate: Long-term results in patients treated with iodine-125 implantation. Int J Radiat Oncol Biol Phys 1991;21: 537– 547.
31 Priestley JB, Beyer DC: Guided brachytherapy for treatment of confined prostate cancer. Urology 1992;40:127–132.
32 Blasko JC, Wallner K, Grimm PD, Ragde H: Prostate-specific antigen based disease control following ultrasound guided iodine-125 implantation for stage T1/T2 prostatic carcinoma. J Urol 1995;154:1096–1099.
33 Wallner KE, Roy J, Harrison L: Tumour control and morbidity following transperineal iodine-125 implantation for stage T1/T2 prostatic carcinoma. J Clin Oncol 1996;14:449–453.
34 Ragde H, Blasko JC, Grimm PD, Kenny GM, Sylvester JE, Hoak DC, Landin K, Cavangh W: Interstitial iodine-125 radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. Cancer 1998;80:442–453.
35 Polascik TJ, Pound CR, DeWeese TL, Walsh PC: Comparison of radical prostatectomy and iodine-125 interstitial radiotherapy for the treatment of clinically localized prostate cancer: A 7-year biochemical (PSA) progression analysis. Urology 1998;51:884–889.
36 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–874.